Protocol C3991010

A Phase 1, Open-Label, 2-Period, 2-Sequence, Crossover Study to Compare the Single-Dose Pharmacokinetics of 2 Different Formulations of PF-07081532 Administered Orally to Adult Participants Who Are Overweight or Obese

Statistical Analysis Plan
(SAP)

Version: 1

Date: 19 Jan 2023

[redacted]

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NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 / 19 Jan 2023	Original 30 Nov 2022	N/A	N/A

2. INTRODUCTION

PF-07081532 is an orally administered, potent and selective GLP-1R agonist in development as adjunct to diet and exercise, to improve glycemic control in T2DM, and for chronic weight management in a population that is overweight with co-morbidities or who have obesity.

The purpose of the study is to evaluate the relative bioavailability following oral administration of 2 formulations of PF-07081532. In Periods 1 and 2, the PK of the formulation projected to be used in future clinical studies (PF-07081532 80 mg immediate release tablet, Formulation B) will be compared with the PK of the current formulation (PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet, Formulation A) in the fasted state in adult participants who are overweight or obese.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3991010.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives and Endpoints

Objectives	***Endpoints***
Cohort 1	
Primary:	***Primary:***
• *To compare the relative bioavailability of PF-07081532 following administration of a single oral dose of Formulation B (Test) compared to Formulation A (Reference) administered in the fasted state to adult participants who are overweight or obese.*	• *Plasma: PF-07081532 AUC_{inf} (as data permit, otherwise AUC_{last}) and C_{max} for Formulations A and B.*

Objectives	***Endpoints***
Secondary:	***Secondary:***
• *To evaluate the safety and tolerability of a single oral dose of PF-07081532 administered in the fasted state to adult participants who are overweight or obese.*	• *Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters.*
Other:	***Other:***

• *To determine additional pharmacokinetic parameters of PF-07081532 following administration of a single oral dose of PF-07081532 as Formulation A (Reference) and Formulation B (Test) in the fasted state to adult participants who are overweight or obese.*	• *Additional plasma PK parameters:*
	  • *AUC_{last}*
	  • *CL/F and V_z/F , as data permit*
	  • *T_{max}*
	  • *Half-life ($t_{½}$), as data permit.*

2.3. Study Design

This is a randomized, open-label, single dose, 2-period, 2-sequence, crossover study. Participants will be screened for participation in this study within 28 days before dosing in Period 1 to confirm that they meet the inclusion/exclusion criteria for this study. A minimum washout of 6 days between the single 80 mg doses (80 mg immediate release tablet for Formulation B, 20 mg immediate release tablet + 60 mg immediate release tablet for Formulation A) administered in each period will be employed. The expected duration of participation from Screening to the Follow-up telephone contact will be approximately 10 weeks.

Approximately 20 participants will be enrolled to ensure at least 14 evaluable participants with PK data.

Table 2. Randomization Schedule

	Period 1	***Period 2***
Sequence 1 (N=10)	*Formulation A*	*Formulation B*
Sequence 2 (N=10)	*Formulation B*	*Formulation A*

Formulation A (Reference) will be administered as PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet, and Formulation B (Test) will be administered as a PF-07081532 80 mg immediate release tablet.

[redacted]

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoints are the plasma PF-07081532 AUC_{inf} (as data permit, otherwise AUC_{last}) and C_{max} for Formulations A (PF-07081532 20 mg + 60 mg) and B (PF-07081532 80 mg). In addition, the test/reference ratios for AUC_{inf} (as data permit, otherwise AUC_{last}) and C_{max} will be derived with Formulation B as the test treatment and Formulation A as the reference treatment.

3.2. Secondary Endpoints

The secondary endpoints are the safety and tolerability data, discussed in Section 3.5.

3.3. Baseline Variables

Baseline characteristics will be collected according to the schedule of activities (SoA) as specified in the protocol.

3.4. Other Endpoints

Other endpoints include additional plasma PK parameters for formulations A and B of PF-07081532 including AUC_{last}, CL/F, V_z/F, T_{max}, and $t_{1/2}$ as data permit.

Plasma PK parameters of PF-07081532 will be derived (as data permit) from the concentration-time data using standard noncompartmental methods as outlined in Table 3. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 3. Plasma PK Parameters

Parameter	***Definition***	***Method of Determination***
AUC_{inf}[a]	*Area under the concentration-time curve from time zero extrapolated to infinity*	$AUC_{last} + (C_{last}*/k_{el})$, *where* $C_{last}*$ *is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis*
AUC_{last}	*Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration* (C_{last}).	*Linear/Log trapezoidal method.*
C_{max}	*Maximum observed concentration*	*Observed directly from data*
T_{max}	*Time for* C_{max}	*Observed directly from data as time of first occurrence*

[redacted]

Table 3. Plasma PK Parameters

Parameter	*Definition*	*Method of Determination*
$t_{½}$[a]	*Terminal half-life*	*$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.*
CL/F[a]	*Apparent clearance*	*$Dose/AUC_{inf}$*
V_z/F[a]	*Apparent volume of distribution*	*$Dose/(AUC_{inf} \times k_{el})$*

a. If data permit.

3.5. Safety Endpoints

The following data are considered in standard safety summaries (see protocol for collection days, baseline assessment, and list of parameters):

- adverse events (AE)
- laboratory data
- vital signs data
- electrocardiogram (ECG) results

3.5.1. Adverse Events

Any adverse events occurring following start of treatment will be considered as treatment emergent adverse event (TEAE). Events that occur during follow-up within the lag time of up to 35 days after the last dose of study intervention will be counted as treatment emergent and attributed to the last treatment taken. The time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol. To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will not take into account whether each participants's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

For both periods, the baseline measurement is the predose measurement on Period 1 Day -1.

[redacted]

3.5.3. Vital Signs

Supine blood pressure (BP) and pulse rate (PR) will be measured at times specified in the SoA given in the protocol.

For both periods, the baseline measurement is the predose measurement on Day 1 in each period.

3.5.4. Electrocardiograms

QT interval, QTcF, PR, QRS and heart rate (HR) will be recorded at each assessment time indicated in the SoA given in the protocol. QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{(1/3)} \text{ where } RR = 60/HR \text{ (if not provided)}$$

For both periods, the baseline measurement is the predose measurement on Day 1 in each period.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	***Description***
Enrolled/Randomly assigned to study intervention	*"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
Safety Analysis Set	*All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.*
PK Concentration Set	*All participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported.*
PK Parameter Set	*All participants who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported. Should vomiting occur after administration of PF-07081532, the resulting PK parameters from that participant from the corresponding period may be excluded.*

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analysis will be performed after study participant data set release following last participant last visit.

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

5.2.1. Analyses for Binary/Categorical Endpoints

For binary or categorical variables, number of participants, numbers and percentages of participants meeting the categorical criteria will be presented in accordance with the Clinical Data Interchange Standards Consortium and Pfizer Standards (CaPS).

5.2.2. Analyses for Continuous Endpoints

For continuous variables, the data will be summarized using the number of participants, mean, median, standard deviation (SD), minimum, and maximum in accordance with the CaPS. For appropriate PK parameters, geometric mean and geometric coefficient of variation (%CV) will also be summarized.

5.3. Methods to Manage Missing Data

5.3.1. Pharmacokinetic Data

Methods to handle missing PK data are described below.

Concentrations Below the Limit of Quantification:

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

Deviations, Missing Concentrations and Anomalous Values:

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample).
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other

participants. For example, a BLQ concentration that is between quantifiable values from the same dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst.

PK Parameters:

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues).

In summary tables, statistics will not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to a dosing error or an unexpected event such as vomiting before all the compound is adequately absorbed from the gastrointestinal tract), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses. For instance, if a participant has a vomiting event post dose that is within a duration of time that is 2-times the derived median T_{max} for the population for the administered treatment, then the pharmacokineticist should consider the exclusion of the PK concentration data collected following the initial vomiting event in that treatment period and the PK parameter data reported for that treatment period from the datasets used to calculate summary statistics or statistical analyses.

5.3.2. Safety Data

Missing values in standard summaries of AEs, laboratory data, vital signs, and ECGs will be imputed according to CaPS.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

AUC_{inf} (if data permit), AUC_{last} and C_{max} will be summarized by treatment group and will include the set of summary statistics as specified in Table 4.

For the evaluation of relative bioavailability, *natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within the sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Formulation A (PF-07081532 20 mg + 60 mg) will be the Reference treatment while Formulation B (PF-07081532 80 mg) will be the Test treatment.*

For AUC_{inf}, AUC_{last} and C_{max}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf}, AUC_{last} and C_{max}, will be plotted by treatment and overlaid with geometric means.

Residuals from the model will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the CSR. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

6.2. Secondary Endpoints

Analyses and summaries of safety data are described in Section 6.6.

6.3. Other Endpoints

6.3.1. PK Concentration

The plasma concentrations of PF-07081532 will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles of the plasma concentration time data will be plotted by treatment using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales.

Presentations of concentrations will include:

- A listing of all concentrations sorted by participant ID, treatment and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by treatment and nominal time postdose, where the set of statistics will include n, mean, median, SD, %CV, minimum, maximum and the number of concentrations above the LLQ.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Individual concentration time plots by treatment (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each treatment per scale).

- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all treatments) per scale].

6.3.2. PK parameter

The PK parameters will be listed and summarized descriptively by treatment group in accordance with Pfizer data standards on the PK Parameter Analysis Set, as data permit. Missing values will be handled as detailed in Section 5.3.1. Each PK parameter will be summarized by treatment group and will include the set of summary statistics as specified in Table 4.

Table 4. PK Parameters to be Summarized Descriptively by Treatment

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, C_{max}, CL/F, V_z/F	N, arithmetic mean, median, SD, %CV, minimum, maximum, geometric mean and geometric %CV
T_{max}	N, median, minimum, maximum
$t_{½}$	N, arithmetic mean, median, SD, %CV, minimum, maximum

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by analyte and group: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation (AUC_{extrap}%); and the first, last, and number of time points used in the estimation of k_{el}. This data may be included in the clinical study report.

6.4. Subset Analyses

There are no planned subset analyses.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Demographic Summaries

Demographic characteristics will be summarized for enrolled population in accordance with the CaPS.

6.5.2. Study Conduct and Participant Disposition

Participants evaluation groups will show end of study participant disposition. Frequency counts will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the CaPS.

6.5.3. Study Treatment Exposure

Study treatment exposure will be listed.

6.5.4. Concomitant Medications and Nondrug Treatments

All prior and concomitant medication(s) as well as non-drug treatment(s) will be reported in the listings.

6.6. Safety Summaries and Analyses

All safety analyses will be performed on the Safety Analysis Set.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

6.6.1. Adverse Events

Adverse events will be reported in accordance with the CaPS.

Participant discontinuations due to adverse events will be detailed by treatment. Data will be reported in accordance with the CaPS.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the CaPS.

6.6.3. Vital Signs

Vital sign data will be databased and available upon request.

6.6.4. Electrocardiograms

ECG data will be databased and available upon request.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

APPENDICES

Appendix 1. SAS Code for Analyses

An example of the PROC MIXED code is provided below:

For the primary objective:

```
proc mixed data=tab.pk;
        class seq period trt participant;
        model l&var = seq period trt/ ddfm=KR;
        random participant(seq) / subject=participant(seq);
        lsmeans trt;
        estimate 'B vs A' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows
A: PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet
(Reference);
B: PF-07081532 80 mg immediate release tablet (Test);      */
```

Appendix 2. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation
AE	adverse event
AUC_{extrap}%	the percent of AUC_{inf} based on extrapolation
AUC_{inf}	area under the concentration-time curve to infinity
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration
BLQ	below the limit of quantitation
BP	blood pressure
CaPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CI	confidence interval
C_{last}	last quantifiable concentration
CL/F	apparent clearance
C_{max}	maximum observed concentration
CSR	clinical study report
ECG	electrocardiogram
GLP-1R	glucagon-like peptide-1 receptor
HR	heart rate
k_{el}	terminal phase rate constant
LLQ	lower limit of quantitation
mg	milligram
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	pulse rate
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
r^2	goodness of fit statistic from the log-linear regression
SAP	statistical analysis plan
SD	single dose; standard deviation
SoA	schedule of activities
$t_{½}$	terminal half-life
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
T_{max}	time for C_{max}
V_z/F	apparent volume of distribution

[redacted]